WEST Search History

DATE: Thursday, November 07, 2002

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
L1	epothilone and (polketide synthase or polyketide synthetase or PKS) and (gene or nucleic acid sequence or DNA or cdna)	36	L1

END OF SEARCH HISTORY

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Search Results - Record(s) 1 through 20 of 36 returned.

1. Document ID: US 20020147197 A1

L1: Entry 1 of 36 File: PGPB Oct 10, 2002

PGPUB-DOCUMENT-NUMBER: 20020147197
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020147197 A1

TITLE: Methods and compositions for enhancing pharmaceutical treatments

PUBLICATION-DATE: October 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Newman, Michael J.	San Diego	CA	US	
Dixon, William Ross	La Jolla	CA	US	

US-CL-CURRENT: 514/235.8; 514/254.05, 514/326, 514/396, 514/397, 514/400

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

2. Document ID: US 20020142401 A1

L1: Entry 2 of 36 File: PGPB Oct 3, 2002

PGPUB-DOCUMENT-NUMBER: 20020142401
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020142401 A1

TITLE: Isolated gene for methylmalonyl CoA epimerase and uses thereof

PUBLICATION-DATE: October 3, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Santi, Daniel	San Francisco	CA	US	
Dayem, Linda	Belmont	CA	US	
Kealey, James	San Rafael	CA	US	

US-CL-CURRENT: 435/76; 435/252.3, 435/320.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

3. Document ID: US 20020137152 A1

L1: Entry 3 of 36 File: PGPB Sep 26, 2002

PGPUB-DOCUMENT-NUMBER: 20020137152
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020137152 A1

TITLE: Fermentation process for epothilones

PUBLICATION-DATE: September 26, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Santi, Daniel	San Francisco	CA	US	
Metcalf, Brian	Moraga	CA	US	
Ashley, Gary	Alameda	CA	US	

US-CL-CURRENT: 435/118; 435/184, 435/252.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 4. Document ID: US 20020128213 A1

L1: Entry 4 of 36 File: PGPB Sep 12, 2002

PGPUB-DOCUMENT-NUMBER: 20020128213
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020128213 A1

TITLE: Sixteen-membered macrolide compounds

PUBLICATION-DATE: September 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Katz, Leonard	Oakland	CA	US	
Ashley, Gary	Alameda	CA	US	
Burlingame, Mark A.	San Francisco	CA	US	
Dong, Steven D.	San Francisco	CA	US	
Fu, Hong	Union City	CA	US	
Li, Yong	Palo Alto	CA	US	
Myles, David C.	Kensington	CA	US	

US-CL-CURRENT: 514/30; 536/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 5. Document ID: US 20020111317 A1

L1: Entry 5 of 36 File: PGPB Aug 15, 2002

PGPUB-DOCUMENT-NUMBER: 20020111317
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020111317 A1

TITLE: Sixteen-membered macrolide compounds

PUBLICATION-DATE: August 15, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Katz, Leonard	Oakland	CA	US	
Ashley, Gary	Alameda	CA	US	

US-CL-CURRENT: 514/28; 536/7.1, 536/7.4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 6. Document ID: US 20020103133 A1

L1: Entry 6 of 36 File: PGPB Aug 1, 2002

PGPUB-DOCUMENT-NUMBER: 20020103133
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020103133 A1

TITLE: Peptidase-cleavable, targeted antineoplastic drugs and their therapeutic use

PUBLICATION-DATE: August 1, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Copeland, Robert A.	Hockessin	DE	US	
Albright, Charles F.	West Chester	PA	US	
Combs, Andrew P.	Kennett Square	PA	US	
Dowling, Randine L.	Wilmington	DE	US	
Graciani, Nilsa R.	Wilmington	DE	US	
Han, Wei	Newark	DE	US	
Higley, C. A.	Newark	DE	US	
Huang, Pearl S.	Lansdale	PA	US	
Yue, Eddy W.	Landenberg	PA	US	
DiMeo, Susan V.	Wilmington	DE	US	

US-CL-CURRENT: 514/16; 514/17, 530/328, 530/329

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 7. Document ID: US 20020094962 A1

L1: Entry 7 of 36 File: PGPB Jul 18, 2002

PGPUB-DOCUMENT-NUMBER: 20020094962
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020094962 A1

TITLE: Motilide compounds

PUBLICATION-DATE: July 18, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Ashley, Gary	Alameda	CA	US	
Metcalf, Brian	Moraga	CA	US	
Tian, Zong-Qiang	Fremont	CA	US	
Santi, Daniel	San Francisco	CA	US	

US-CL-CURRENT: 514/28; 536/17.4, 536/7.4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 8. Document ID: US 20020065295 A1

L1: Entry 8 of 36 File: PGPB May 30, 2002

PGPUB-DOCUMENT-NUMBER: 20020065295
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020065295 A1

TITLE: Novel polyketide derivatives

PUBLICATION-DATE: May 30, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Chu, Daniel	Santa Clara	CA	US	
Fardis, Maria	San Carlos	CA	US	
Khosla, Chaitan	Palo Alto	CA	US	
Reeves, Christopher	Orinda	CA	US	
Santi, Daniel	San Francisco	CA	US	
Schirmer, Andreas	Hayward	CA	US	

US-CL-CURRENT: 514/291; 540/456

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 9. Document ID: US 20020052028 A1

L1: Entry 9 of 36 File: PGPB May 2, 2002

PGPUB-DOCUMENT-NUMBER: 20020052028
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020052028 A1

TITLE: Bio-intermediates for use in the chemical synthesis of polyketides

PUBLICATION-DATE: May 2, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Santi, Daniel	San Francisco	CA	US	
Ashley, Gary	Alameda	CA	US	
Myles, David C.	Kensington	CA	US	

US-CL-CURRENT: 435/76; 435/118

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 10. Document ID: US 20020051998 A1

L1: Entry 10 of 36 File: PGPB May 2, 2002

PGPUB-DOCUMENT-NUMBER: 20020051998
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020051998 A1

TITLE: Directed evolution of biosynthetic and biodegradation pathways

PUBLICATION-DATE: May 2, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Schmidt-Dannert, Claudia	Shoreview	MN	US	
Arnold, Frances H.	Pasadena	CA	US	

US-CL-CURRENT: 435/7.1; 435/325, 435/410, 435/67

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 11. Document ID: US 20020045609 A1

L1: Entry 11 of 36 File: PGPB Apr 18, 2002

PGPUB-DOCUMENT-NUMBER: 20020045609
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020045609 A1

TITLE: Epothilone derivatives and methods for making and using the same

PUBLICATION-DATE: April 18, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Ashley, Gary	Alameda	CA	US	
Fardis, Maria	San Carlos	CA	US	
Santi, Daniel	San Francisco	CA	US	

US-CL-CURRENT: 514/183; 514/450, 540/451, 549/270

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 12. Document ID: US 20020045220 A1

L1: Entry 12 of 36 File: PGPB Apr 18, 2002

PGPUB-DOCUMENT-NUMBER: 20020045220
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020045220 A1

TITLE: Biosynthesis of polyketide synthase substrates

PUBLICATION-DATE: April 18, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Khosla, Chaitan	Palo Alto	CA	US	
Pfeifer, Blaine	Stan Ford	CA	US	

US-CL-CURRENT: 435/76; 435/252.3, 435/252.33, 536/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 13. Document ID: US 20020025936 A1

L1: Entry 13 of 36 File: PGPB Feb 28, 2002

PGPUB-DOCUMENT-NUMBER: 20020025936
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020025936 A1

TITLE: Motilide compounds

PUBLICATION-DATE: February 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Ashley, Gary	Alameda	CA	US	
Burlingame, Mark	San Francisco	CA	US	
Carreras, Christopher	Belmont	CA	US	
Santi, Daniel	San Francisco	CA	US	

US-CL-CURRENT: 514/28; 536/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 14. Document ID: US 20020010328 A1

L1: Entry 14 of 36 File: PGPB Jan 24, 2002

PGPUB-DOCUMENT-NUMBER: 20020010328
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020010328 A1

TITLE: Polyketide synthase enzymes and recombinant DNA constructs therefor

PUBLICATION-DATE: January 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Reeves, Christopher	Orinda	CA	US	
Chu, Daniel	Santa Clara	CA	US	
Khosla, Chaitan	Palo Alto	CA	US	
Santi, Daniel	San Francisco	CA	US	
Wu, Kai	Foster City	CA	US	

US-CL-CURRENT: 540/456; 435/183, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 15. Document ID: US 20020004229 A1

L1: Entry 15 of 36 File: PGPB Jan 10, 2002

PGPUB-DOCUMENT-NUMBER: 20020004229
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020004229 A1

TITLE: Overproduction hosts for biosynthesis of polyketides

PUBLICATION-DATE: January 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Santi, Daniel	San Francisco	CA	US	
McDaniel, Robert	Palo Alto	CA	US	
Tang, Li	Foster City	CA	US	
Khosla, Chaitan	Palo Alto	CA	US	

US-CL-CURRENT: 435/76; 435/254.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 16. Document ID: US 20010051356 A1

L1: Entry 16 of 36 File: PGPB Dec 13, 2001

PGPUB-DOCUMENT-NUMBER: 20010051356
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010051356 A1

TITLE: Methods for making polyketides

PUBLICATION-DATE: December 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Khosla, Chaitan	Stanford	CA	US	
Lau, Janice	Stanford	CA	US	
Pohl, Nicola L.	Menlo Park	CA	US	

US-CL-CURRENT: 435/41; 435/148, 435/193, 435/64, 435/76

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 17. Document ID: US 6410301 B1

L1: Entry 17 of 36 File: USPT Jun 25, 2002

US-PAT-NO: 6410301
DOCUMENT-IDENTIFIER: US 6410301 B1

TITLE: Myxococcus host cells for the production of epothilones

DATE-ISSUED: June 25, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Julien; Bryan	Oakland	CA		
Katz; Leonard	Hayward	CA		
Khosla; Chaitan	Palo Alto	CA		

US-CL-CURRENT: 435/252.3

ABSTRACT:

Recombinant Myxococcus host cell containing recombinant expression vectors containing epothilone polyketide synthase genes can produce epothilones C and D.

6 Claims, 4 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 18. Document ID: US 6399789 B1

L1: Entry 18 of 36 File: USPT Jun 4, 2002

US-PAT-NO: 6399789
DOCUMENT-IDENTIFIER: US 6399789 B1

TITLE: Multi-plasmid method for preparing large libraries of polyketides and non-ribosomal peptides

DATE-ISSUED: June 4, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Santi; Daniel V.	San Francisco	CA		
Xue; Qun	San Francisco	CA		
Ashley; Gary	Alameda	CA		

US-CL-CURRENT: 549/271; 536/4.1

ABSTRACT:

A multiple-plasmid system for heterologous expression of polyketides facilitates combinatorial biosynthesis. The method can be extended to any modular polyketide synthase (PKS) or non-ribosomal peptide synthase (NRPS) and has the potential to produce thousands of novel natural products, including ones derived from further modification of the PKS or NRPS products by tailoring enzymes.

11 Claims, 11 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 9

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 19. Document ID: US 6383787 B1

L1: Entry 19 of 36 File: USPT May 7, 2002

US-PAT-NO: 6383787
DOCUMENT-IDENTIFIER: US 6383787 B1

TITLE: Genes for the biosynthesis of epothilones

DATE-ISSUED: May 7, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schupp; Thomas	Mohlin			CH
Ligon; James Madison	Apex	NC		
Molnar; Istvan	Durham	NC		
Zirkle; Ross	Raleigh	NC		
Cyr; Devon Dawn	Fuquay-Varina	NC		
Gorlach; Jorn	Durham	NC		

US-CL-CURRENT: 435/183; 435/193, 435/252.3, 435/252.35, 435/320.1, 536/23.1, 536/23.2, 536/23.7

ABSTRACT:

Nucleic acid molecules are isolated from Sorangium cellulosum that encode polypeptides necessary for the biosynthesis of epothilone. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

25 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 20. Document ID: US 6358719 B1

L1: Entry 20 of 36 File: USPT Mar 19, 2002

US-PAT-NO: 6358719
DOCUMENT-IDENTIFIER: US 6358719 B1

TITLE: Genes for the biosynthesis of epothilones

DATE-ISSUED: March 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schupp; Thomas	Mohlin			CH
Ligon; James Madison	Apex	NC		
Molnar; Istvan	Durham	NC		
Zirkle; Ross	Raleigh	NC		
Cyr; Devon Dawn	Fuquay-Varina	NC		
Gorlach; Jorn	Durham	NC		

US-CL-CURRENT: 435/189; 435/252.3, 435/252.35, 435/320.1, 536/23.1, 536/23.2, 536/23.7

ABSTRACT:

Nucleic acid molecules are isolated from Sorangium cellulosum that encode polypeptides necessary for the biosynthesis of epothilone. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

25 Claims, 0 Drawing figures
Exemplary Claim Number: 1

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Search Results - Record(s) 21 through 36 of 36 returned.

☐ 21. Document ID: US 6355459 B1

L1: Entry 21 of 36 File: USPT Mar 12, 2002

US-PAT-NO: 6355459
DOCUMENT-IDENTIFIER: US 6355459 B1

TITLE: Genes for the biosynthesis of epothilones

DATE-ISSUED: March 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schupp; Thomas	Mohlin			CH
Ligon; James Madison	Apex	NC		
Molnar; Istvan	Durham	NC		
Zirkle; Ross	Raleigh	NC		
Cyr; Devon Dawn	Fuquay-Varina	NC		
Gorlach; Jorn	Durham	NC		

US-CL-CURRENT: 435/183; 435/189, 435/193, 435/232, 435/252.3, 435/252.35, 435/320.1, 536/23.2

ABSTRACT:

Nucleic acid molecules are isolated from Sorangium cellulosum that encode polypeptides necessary for the biosynthesis of epothilone. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

115 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 22. Document ID: US 6355458 B1

L1: Entry 22 of 36 File: USPT Mar 12, 2002

US-PAT-NO: 6355458
DOCUMENT-IDENTIFIER: US 6355458 B1

TITLE: Genes for the biosynthesis of epothilones

DATE-ISSUED: March 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schupp; Thomas	Mohlin			CH
Ligon; James Madison	Apex	NC		
Molnar; Istvan	Durham	NC		
Zirkle; Ross	Raleigh	NC		
Cyr; Devon Dawn	Fuquay-Varina	NC		
Gorlach; Jorn	Durham	NC		

US-CL-CURRENT: 435/183; 435/189, 435/193, 435/232, 435/252.3, 435/252.35, 435/320.1, 530/300, 536/23.1, 536/23.2, 536/23.7

ABSTRACT:

Nucleic acid molecules are isolated from Sorangium cellulosum that encode polypeptides necessary for the biosynthesis of epothilone. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

100 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 23. Document ID: US 6355457 B1

L1: Entry 23 of 36 File: USPT Mar 12, 2002

US-PAT-NO: 6355457
DOCUMENT-IDENTIFIER: US 6355457 B1

TITLE: Genes for the biosynthesis of epothilones

DATE-ISSUED: March 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schupp; Thomas	Mohlin			CH
Ligon; James Madison	Apex	NC		
Molnar; Istvan	Durham	NC		
Zirkle; Ross	Raleigh	NC		
Cyr; Devon Dawn	Fuquay-Varina	NC		
Gorlach; Jorn	Durham	NC		

US-CL-CURRENT: 435/183; 435/189, 435/193, 435/195, 435/196, 435/232, 435/252.3, 435/252.35, 435/320.1, 530/300, 536/23.1 , 536/23.2, 536/23.7

ABSTRACT:

Nucleic acid molecules are isolated from Sorangium cellulosum that encode polypeptides necessary for the biosynthesis of epothilone. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

115 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 24. Document ID: US 6346404 B1

L1: Entry 24 of 36 File: USPT Feb 12, 2002

US-PAT-NO: 6346404
DOCUMENT-IDENTIFIER: US 6346404 B1

TITLE: Genes for the biosynthesis of epothilones

DATE-ISSUED: February 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schupp; Thomas	Mohlin			CH
Ligon; James Madison	Apex	NC		
Molnar; Istvan	Durham	NC		
Zirkle; Ross	Raleigh	NC		
Cyr; Devon Dawn	Fuquay-Varina	NC		
Gorlach; Jorn	Durham	NC		

US-CL-CURRENT: 435/183; 435/189, 435/193, 435/232, 435/252.3, 435/252.35, 435/320.1, 530/350, 536/23.1, 536/23.2, 536/23.7

ABSTRACT:

Nucleic acid molecules are isolated from Sorangium cellulosum that encode polypeptides necessary for the biosynthesis of epothilone. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

85 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 25. Document ID: US 6303767 B1

L1: Entry 25 of 36 File: USPT Oct 16, 2001

US-PAT-NO: 6303767
DOCUMENT-IDENTIFIER: US 6303767 B1

TITLE: Nucleic acids encoding narbonolide polyketide synthase enzymes from streptomyces narbonensis

DATE-ISSUED: October 16, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Betlach; Melanie C.	San Francisco	CA		
McDaniel; Robert	Palo Alto	CA		

US-CL-CURRENT: 536/23.2; 435/320.1, 536/23.1

ABSTRACT:

Host cells comprising recombinant vectors encoding the narbomycin polyketide synthase and narbomycin modification enzymes from Streptomyces narbonensis can be used to produce narbomycin, picromycin, methymycin, and neomethymycin. Recombinant DNA constructs comprising one or more narbomycin polyketide synthase domains, modules, open reading frames, and variants thereof can be used to produce recombinant polyketide synthases and a variety of different polyketides with application in agriculture, medicine, and animal health.

9 Claims, 2 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 26. Document ID: US 6303342 B1

L1: Entry 26 of 36 File: USPT Oct 16, 2001

US-PAT-NO: 6303342
DOCUMENT-IDENTIFIER: US 6303342 B1

TITLE: Recombinant methods and materials for producing epothilones C and D

DATE-ISSUED: October 16, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Julien; Bryan	Oakland	CA		
Katz; Leonard	Hayward	CA		
Khosla; Chaitan	Palo Alto	CA		
Tang; Li	Foster City	CA		

US-CL-CURRENT: 435/76

ABSTRACT:

Recombinant nucleic acids that encode all or a portion of the epothilone polyketide synthase (PKS) are used to express recombinant PKS genes in host cells for the production of epothilones, epothilone derivatives, and polyketides that are useful as cancer chemotherapeutics, fungicides, and immunosuppressants.

29 Claims, 9 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 8

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 27. Document ID: US 6280999 B1

L1: Entry 27 of 36 File: USPT Aug 28, 2001

US-PAT-NO: 6280999
DOCUMENT-IDENTIFIER: US 6280999 B1

TITLE: Sorangium polyketide synthases and encoding DNA therefor

DATE-ISSUED: August 28, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gustafsson; Claes	Belmont	CA		
Betlach; Mary C.	San Francisco	CA		
Ashley; Gary	Alameda	CA		
Julien; Bryan	Oakland	CA		
Ziermann; Rainer	San Mateo	CA		

US-CL-CURRENT: 435/252.3; 435/183, 435/320.1, 435/325, 536/23.2

ABSTRACT:

Novel Sorangium polyketide synthases, and domains thereof, and polynucleotides encoding therefor. Additionally, chimeric polyketide synthases that include domains, or subsets of domains, patterned on said novel polyketide synthases. Methods to prepare polyketide combinatorial libraries are described, as are recombinant host cells in which polyketides are produced.

8 Claims, 7 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 21

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 28. Document ID: US 6251636 B1

L1: Entry 28 of 36 File: USPT Jun 26, 2001

US-PAT-NO: 6251636
DOCUMENT-IDENTIFIER: US 6251636 B1

TITLE: Recombinant oleandolide polyketide synthase

DATE-ISSUED: June 26, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Betlach; Mary C.	San Francisco	CA		
Shah; Sanjay Krishnakant	Concord	CA		
McDaniel; Robert	Palo Alto	CA		
Tang; Li	Foster City	CA		

US-CL-CURRENT: 435/76; 435/252.35, 435/254.2, 435/320.1, 435/325, 435/419, 536/23.1, 536/23.2

ABSTRACT:

Recombinant DNA compounds that encode all or a portion of the oleandolide polyketide synthase are used to express recombinant polyketide synthase genes in host cells for the production of oleandolide, oleandolide derivatives, and polyketides that are useful as antibiotics and motilides.

22 Claims, 5 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 29. Document ID: US 6221641 B1

L1: Entry 29 of 36 File: USPT Apr 24, 2001

US-PAT-NO: 6221641
DOCUMENT-IDENTIFIER: US 6221641 B1

TITLE: Method for making polyketides

DATE-ISSUED: April 24, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Khosla; Chaitan	Stanford	CA		
Lau; Janice	Stanford	CA		
Pohl; Nicola L.	Menlo Park	CA		

US-CL-CURRENT: 435/193; 435/69.1

ABSTRACT:

The stereochemical centers of a polyketide can be changed by replacement of ketosynthase domains in the polyketide synthase (PKS) enzyme that produces the polyketide. The specificity of the AT domains of a PKS is determined by a hypervariable region that can be replaced or altered to change the specificity of the AT domain from a naturally occurring extender unit to another naturally or non-naturally occurring extender unit. Non-naturally occurring extender units, including methylmalonyl N-acetyl cysteamine thioester can be incorporated into polyketides in recombinant host cells or in cell-free systems to make polyketides.

13 Claims, 3 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 30. Document ID: US 6121029 A

L1: Entry 30 of 36 File: USPT Sep 19, 2000

US-PAT-NO: 6121029
DOCUMENT-IDENTIFIER: US 6121029 A

TITLE: Genes for the biosynthesis of epothilones

DATE-ISSUED: September 19, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schupp; Thomas	Mohlin			CH
Ligon; James Madison	Apex	NC		
Molnar; Istvan	Durham	NC		
Zirkle; Ross	Raleigh	NC		
Cyr; Devon Dawn	Fuquay-Varina	NC		
Gorlach; Jorn	Durham	NC		

US-CL-CURRENT: 435/183; 435/189, 435/193, 435/232, 435/252.3, 435/252.35, 435/320.1, 530/300, 536/23.1, 536/23.2, 536/23.7

ABSTRACT:

Nucleic acid molecules are isolated from Sorangium cellulosum that encode polypeptides necessary for the biosynthesis of epothilone. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

115 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 31. Document ID: US 6117659 A

L1: Entry 31 of 36 File: USPT Sep 12, 2000

US-PAT-NO: 6117659
DOCUMENT-IDENTIFIER: US 6117659 A

TITLE: Recombinant narbonolide polyketide synthase

DATE-ISSUED: September 12, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ashley; Gary	Alameda	CA		
Betlach; Melanie C.	Burlingame	CA		
Betlach; Mary	San Francisco	CA		
McDaniel; Robert	Palo Alto	CA		
Tang; Li	Foster City	CA		

US-CL-CURRENT: 435/155; 435/132, 435/189, 435/252.3, 435/252.33, 435/252.35, 435/320.1, 536/23.2, 536/23.7

ABSTRACT:

Recombinant DNA compounds that encode all or a portion of the narbonolide polyketide synthase are used to express recombinant polyketide synthase genes in host cells for

the production of narbonolide, narbonolide derivatives, and polyketides that are useful as antibiotics and as intermediates in the synthesis of compounds with pharmaceutical value.

11 Claims, 9 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 32. Document ID: US 6090601 A

L1: Entry 32 of 36 File: USPT Jul 18, 2000

US-PAT-NO: 6090601
DOCUMENT-IDENTIFIER: US 6090601 A

TITLE: Sorangium polyketide synthase

DATE-ISSUED: July 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gustafsson; Claes	Belmont	CA		
Betlach; Mary C.	San Francisco	CA		

US-CL-CURRENT: 435/183; 435/252.3, 435/320.1, 435/325, 536/23.2

ABSTRACT:

Domains of epothilone polyketide synthase, and polynucleotides encoding therefor. Additionally, chimeric polyketide synthases that include domains, or subsets of domains, patterned on epothilone polyketide synthase. Methods to prepare epothilone in pharmaceutically useful quantitites are described, as are methods to prepare polyketide combinatorial libraries.

24 Claims, 12 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 13

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

☐ 33. Document ID: WO 22139 A2

L1: Entry 33 of 36 File: EPAB Apr 20, 2000

PUB-NO: WO000022139A2
DOCUMENT-IDENTIFIER: WO 22139 A2
TITLE: DNA SEQUENCES FOR ENZYMATIC SYNTHESIS OF POLYKETIDE OR HETEROPOLYKETIDE COMPOUNDS

PUBN-DATE: April 20, 2000

INVENTOR-INFORMATION:

NAME	COUNTRY
BEYER, STEFAN	DE
BLOECKER, HELMUT	DE
BRANDT, PETRA	DE
CINO, PAUL M	US
DOUGHERTY, BRIAN A	US
GOLDBERG, STEVEN L	US
HOFLE, GERHARD	DE
MUELLER, ROLF-JOACHIM	DE
REICHENBACH, HANS	DE

INT-CL (IPC): C12 N 15/52; C12 N 9/00; C12 N 15/63; C12 N 5/10; C12 P 17/06

ABSTRACT:

CHG DATE=20001128 STATUS=O>The invention consists of: (1) cloned Sorangium cellulosum polyketide synthase (PKS) biosynthetic cluster DNA; and (2) the nucleotide sequence and predicted protein coding sequences of the cloned DNA. The invention can be used for, but not limited to: (a) increasing yields of PKS product in Sorangium cellulosum (e.g., by amplification or genetic modification of the epothilone gene cluster or its component parts); (b) increasing yields of polyketide product in a heterologous system by transfer of the epothilone gene cluster or its component parts, which may be followed by amplification or genetic modification of the PKS gene cluster or its component parts; (c) modification of the polyketide product chemical structure in either Sorangium cellulosum or a heterologous host (e.g., by genetic modification of the epothilone gene cluster or its component parts; and (d) for the detection of genes and gene products involved in making polyketides or related molecules in other organisms (e.g., by hybridization or complementation assays). DNA sequence and analysis is presented for the following cosmids and plasmids: A2 cosmid; the pEPOcos6 region (overlapping of pEPOcos6 and pEPOcos7); pEPOcos8 cosmid; A5 cosmid; Sau4 (10 kb plasmid).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 34. Document ID: WO 200183800 A2 AU 200195195 A

L1: Entry 34 of 36 File: DWPI Nov 8, 2001

DERWENT-ACC-NO: 2002-075167
DERWENT-WEEK: 200246
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TITLE: Recombinant host cells useful for producing polyketides e.g. epothilone or its derivatives, comprises a recombinant expression vector encoding a heterologous polyketide synthase gene

INVENTOR: ARSLANIAN, R L; ASHLEY, G ; FRYKMAN, S ; JULIEN, B ; KATZ, L ; KHOSLA, C ; LAU, J ; LICARDI, P J ; REGENTIN, R ; SANTI, D ; TANG, L

PRIORITY-DATA: 2001US-269020P (April 13, 2001), 2000US-0560367 (April 28, 2000), 2000US-232696P (September 14, 2000), 2000US-257517P (December 21, 2000), 2001US-0825856 (April 3, 2001), 2001US-0825876 (April 3, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200183800 A2	November 8, 2001	E	221	C12P017/00
AU 200195195 A	November 12, 2001		000	C12P017/00

INT-CL (IPC): C12 P 17/00

ABSTRACTED-PUB-NO: WO 200183800A
BASIC-ABSTRACT:

NOVELTY - A recombinant host cell, (I), of the suborder Cystobacterineae comprising a recombinant expression vector encoding a heterologous polyketide synthase (PKS) gene and produces a polyketide synthesized by the PKS enzyme encoded on the vector, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an epothilone derivative of formula (II) produced by culturing (I) with a diketide equivalent compound of formula (III);

(2) purifying (M1) an epothilone from a cell that produces epothilone, comprises culturing the cell in the presence of XAD resin, eluting epothilone from the resin, performing a solid phase extraction of epothilone eluted from the resin, and performing chromatography on epothilone resulting from the solid phase extraction;

(3) crystalline epothilone D obtained after purification of epothilone from a cell;

(4) fermentation (M2) of a Myxococcus host cell, comprising culturing the cell in liquid medium comprising a fatty acid or oil as a carbon source; and

(5) an isolated compound of formula (IV).

R1, R2, R3, R5, R11, and R12 = hydrogen, methyl, or ethyl;

R4, R6 and R9 = hydrogen, hydroxyl, or oxo;

R5 and R6 = together from a carbon carbon double bond;

R7 = hydrogen, methyl, or ethyl;

R8 and R10 = both hydrogen or together from a carbon carbon double bond or an epoxide;

Ar = aryl;

W = O or NR13;

R13 = hydrogen, 1-10C aliphatic, aryl or alkylaryl;

R7a = hydrogen or methyl; and

Ary = aryl selected from formulas of (1)-(26);

R = hydrogen, hydroxy, halogen, amino, 1-5C alkyl, 1-5C hydroxyalkyl, 1-5C alkoxy, and 1-5C aminoalkyl.

ACTIVITY - Cytostatic; antipsoriatic; antiarthritic; antiarteriosclerotic; antiinflammatory; neuroprotective; vasotropic.

MECHANISM OF ACTION - Modulator.

USE - (I) is useful for producing a polyketide. (M1) is also useful for treating cancer, hyperproliferative diseases and conditions such as psoriasis, inflammation, sarcomas, neoplasms, lymphomas, multiple sclerosis, rheumatoid arthritis, atherosclerosis and/or restenosis. It improves polyketide production in any organism and also for production of products of recombinant PKS genes and modification enzymes.

ADVANTAGE - The host cell produces epothilones or epothilone derivatives that is easier to manipulate and ferment than the natural producer Sorangium cellulosum and that produces more of the desired polyketide product. (I) produces polyketides as high levels and are useful in the production of not only epothilones, including new epothilone derivatives, but also other polyketides.

☐ 35. Document ID: US 6090601 A

L1: Entry 35 of 36 File: DWPI Jul 18, 2000

DERWENT-ACC-NO: 2000-498261
DERWENT-WEEK: 200170
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TITLE: Novel epothilone polyketide synthase comprising a ketoreductase or ketosynthase domain, useful for producing epothilone

INVENTOR: BETLACH, M C; GUSTAFSSON, C

PRIORITY-DATA: 1998US-0010809 (January 23, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 6090601 A	July 18, 2000		039	C12N009/00

INT-CL (IPC): C07 H 21/04; C12 N 1/20; C12 N 5/00; C12 N 9/00; C12 N 15/00

ABSTRACTED-PUB-NO: US 6090601A
BASIC-ABSTRACT:

NOVELTY - A polyketide synthase (PKS) (I) comprising a ketoreductase or ketosynthase domain which comprise a peptide sequence, is new. The peptide sequence is a subset of the 159 (S1), 250 (S3) or 197 (S5) amino acid sequence defined in the specification.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a chimeric PKS (II) that comprises one or more epothilone PKS domains with a 260 (S7), 249 (S8), 222 (S9) or 264 (S10) amino acid sequence defined in the specification, or their subsets comprising 10 consecutive amino acids, or the sequence of (S5), (S3) or (S1);

(2) a purified and isolated DNA molecule (III) encoding a PKS domain, comprising the fully defined sequence of 477 (S2), 751 (S4), 591 (S6), 787 (S11), 750 (S12), 667 (S13), or 794 (S14) nucleotides as given in the specification;

(3) a purified and isolated DNA molecule (IV) comprising an open reading frame of (S2) or a specific nucleotide sequence defined in the specification which codes for (I) or its continuous subset that codes for at least 10 amino acid residues of (I);

(4) a polynucleotide that is complementary to (III);

(5) a recombinant expression system (V) capable of expressing (I) or (II) in which the coding sequence is operably linked to control sequences effective in the cell;

(6) a host cell (VI) modified to contain (V); and

(7) preparation of PKS domain, comprising culturing (VI) under conditions such that PKS domain is expressed.

USE - (I) is useful for preparing epothilone in large quantities which is useful as an antitumor agent.

☐ 36. Document ID: WO 200031247 A2 AU 200017377 A EP 1135470 A2 US 6303342 B1 KR 2001093103 A CN 1333820 A US 6410301 B1

L1: Entry 36 of 36 File: DWPI Jun 2, 2000

DERWENT-ACC-NO: 2000-400061
DERWENT-WEEK: 200246
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TITLE: Novel DNA molecules encoding modified epothilones useful in the treatment of tumors

INVENTOR: JULIEN, B; KATZ, L ; KHOSLA, C ; TANG, L ; ZIERMANN, R

PRIORITY-DATA: 1999US-130560P (April 22, 1999), 1998US-109401P (November 20, 1998), 1999US-119386P (February 10, 1999), 1999US-122620P (March 3, 1999), 1999US-0443501 (November 19, 1999), 2000US-0560367 (April 28, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200031247 A2	June 2, 2000	E	136	C12N015/00
AU 200017377 A	June 13, 2000		000	C12N015/00
EP 1135470 A2	September 26, 2001	E	000	C12N009/00
US 6303342 B1	October 16, 2001		000	C12P019/62
KR 2001093103 A	October 27, 2001		000	C12N015/52
CN 1333820 A	January 30, 2002		000	C12N009/00
US 6410301 B1	June 25, 2002		000	C12N001/20

INT-CL (IPC): C12 N 1/20; C12 N 9/00; C12 N 15/00; C12 N 15/52; C12 P 17/06; C12 P 19/62

ABSTRACTED-PUB-NO: US 6303342B
BASIC-ABSTRACT:

NOVELTY - An isolated recombinant nucleic acid (I) comprising a sequence encoding at least a domain of epothilone polyketide synthase (PKS) and/or a functional region of an epothilone modification enzyme.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a recombinant DNA vector comprising (I) ;

(2) producing a polyketide comprising culturing the cells in (2);

(3) a recombinant Sorangium cellulosum comprising a mutated gene for an epothilone PKS protein or epothilone modification enzyme, the gene being inserted into the genome of the cell following homologous recombination with a vector comprising all or part of the gene;

(4) recombinant Myxococcus or Streptomyces cells expressing a gene for an epothilone PKS protein or epothilone modification enzyme, optionally comprising one or more epothilone PKS protein or epothilone modification enzyme genes integrated into their chromosomal DNA and/or one or more epothilone modification enzyme genes on an extrachromosomal expression vector;

(5) producing epothilone or derivative comprising culturing the cells in (5);

(6) a modified epothilone PKS with a modification comprising:

(i) replacement of at least one AT domain with an AT domain of a different specificity;

(ii) inactivation of the NRPS-like module 1 or of the KS2 catalytic domain;

(iii) inactivation of at least one activity in at least one beta -carbonyl modification

domain;

(iv) addition of at least one of KR, DH and ER activity in at least one beta -carbonyl modification domain; and

(v) replacement of the NRPS module 1 with a NRPS of a different specificity;

(7) preparing an epothilone derivative comprising providing substrates including extender units to the modified PKS in (7);

(8) an epothilone PKS modified by inactivation of the NRPS of module 1 or the KS2 of module 2;

(9) preparing an epothilone derivative comprising contacting (9) with a module 2 or 3 substrate and extender units;

(10) host cells comprising (I), (6) or (8);

(11) 16-desmethyl epothilones, 14-methyl epothilones, 11-hydroxyl epothilones, 10-methyl epothilones, 8,9-anhydro epothilones, 9-keto epothilones, 8-desmethyl epothilones and 6-desmethyl epothilones; and

(12) a recombinant PKS enzyme comprising one or more domains, modules or proteins of a non-epothilone PKS and one or more domains, modules or proteins from a epothilone PKS and/or a loading domain comprising a KSQ domain.

USE - The recombinant DNA molecules are useful in the synthesis of the epothilones A, B, C and D. These compounds are useful in the treatment of certain cancers.
ABSTRACTED-PUB-NO:

US 6410301B EQUIVALENT-ABSTRACTS:

NOVELTY - An isolated recombinant nucleic acid (I) comprising a sequence encoding at least a domain of epothilone polyketide synthase (PKS) and/or a functional region of an epothilone modification enzyme.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a recombinant DNA vector comprising (I) ;

(2) producing a polyketide comprising culturing the cells in (2);

(3) a recombinant Sorangium cellulosum comprising a mutated gene for an epothilone PKS protein or epothilone modification enzyme, the gene being inserted into the genome of the cell following homologous recombination with a vector comprising all or part of the gene;

(4) recombinant Myxococcus or Streptomyces cells expressing a gene for an epothilone PKS protein or epothilone modification enzyme, optionally comprising one or more epothilone PKS protein or epothilone modification enzyme genes integrated into their chromosomal DNA and/or one or more epothilone modification enzyme genes on an extrachromosomal expression vector;

(5) producing epothilone or derivative comprising culturing the cells in (5);

(6) a modified epothilone PKS with a modification comprising:

(i) replacement of at least one AT domain with an AT domain of a different specificity;

(ii) inactivation of the NRPS-like module 1 or of the KS2 catalytic domain;

(iii) inactivation of at least one activity in at least one beta -carbonyl modification domain;

(iv) addition of at least one of KR, DH and ER activity in at least one beta -carbonyl modification domain; and

(v) replacement of the NRPS module 1 with a NRPS of a different specificity;

(7) preparing an epothilone derivative comprising providing substrates including extender units to the modified PKS in (7);

(8) an epothilone PKS modified by inactivation of the NRPS of module 1 or the KS2 of module 2;

(9) preparing an epothilone derivative comprising contacting (9) with a module 2 or 3 substrate and extender units;

(10) host cells comprising (I), (6) or (8);

(11) 16-desmethyl epothilones, 14-methyl epothilones, 11-hydroxyl epothilones, 10-methyl epothilones, 8,9-anhydro epothilones, 9-keto epothilones, 8-desmethyl epothilones and 6-desmethyl epothilones; and

(12) a recombinant PKS enzyme comprising one or more domains, modules or proteins of a non-epothilone PKS and one or more domains, modules or proteins from a epothilone PKS and/or a loading domain comprising a KSQ domain.

USE - The recombinant DNA molecules are useful in the synthesis of the epothilones A, B, C and D. These compounds are useful in the treatment of certain cancers.

NOVELTY - An isolated recombinant nucleic acid (I) comprising a sequence encoding at least a domain of epothilone polyketide synthase (PKS) and/or a functional region of an epothilone modification enzyme.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a recombinant DNA vector comprising (I) ;

(2) producing a polyketide comprising culturing the cells in (2);

(3) a recombinant Sorangium cellulosum comprising a mutated gene for an epothilone PKS protein or epothilone modification enzyme, the gene being inserted into the genome of the cell following homologous recombination with a vector comprising all or part of the gene;

(4) recombinant Myxococcus or Streptomyces cells expressing a gene for an epothilone PKS protein or epothilone modification enzyme, optionally comprising one or more epothilone PKS protein or epothilone modification enzyme genes integrated into their chromosomal DNA and/or one or more epothilone modification enzyme genes on an extrachromosomal expression vector;

(5) producing epothilone or derivative comprising culturing the cells in (5);

(6) a modified epothilone PKS with a modification comprising:

(i) replacement of at least one AT domain with an AT domain of a different specificity;

(ii) inactivation of the NRPS-like module 1 or of the KS2 catalytic domain;

(iii) inactivation of at least one activity in at least one beta -carbonyl modification domain;

(iv) addition of at least one of KR, DH and ER activity in at least one beta -carbonyl modification domain; and

(v) replacement of the NRPS module 1 with a NRPS of a different specificity;

(7) preparing an epothilone derivative comprising providing substrates including extender units to the modified PKS in (7);

(8) an epothilone PKS modified by inactivation of the NRPS of module 1 or the KS2 of module 2;

(9) preparing an epothilone derivative comprising contacting (9) with a module 2 or 3 substrate and extender units;

(10) host cells comprising (I), (6) or (8);

(11) 16-desmethyl epothilones, 14-methyl epothilones, 11-hydroxyl epothilones, 10-methyl epothilones, 8,9-anhydro epothilones, 9-keto epothilones, 8-desmethyl epothilones and 6-desmethyl epothilones; and

(12) a recombinant PKS enzyme comprising one or more domains, modules or proteins of a non-epothilone PKS and one or more domains, modules or proteins from a epothilone PKS and/or a loading domain comprising a KSQ domain.

USE - The recombinant DNA molecules are useful in the synthesis of the epothilones A, B, C and D. These compounds are useful in the treatment of certain cancers.

WO 200031247A

Generate Collection Print

Terms	Documents
epothilone and (polketide synthase or polyketide synthetase or PKS) and (gene or nucleic acid sequence or DNA or cdna)	36

Display Format: - Change Format

Previous Page Next Page

```
=> file .nash
=> s epothilone and (polyketide synthase or polyketide synthetase)
L1          14 FILE MEDLINE
L2          31 FILE CAPLUS
L3          14 FILE SCISEARCH
L4           4 FILE LIFESCI
L5          13 FILE BIOSIS
L6          14 FILE EMBASE

TOTAL FOR ALL FILES
L7          90 EPOTHILONE AND (POLYKETIDE SYNTHASE OR POLYKETIDE SYNTHETASE)

=> s l7 and epod
TOTAL FOR ALL FILES
L14          7 L7 AND EPOD

=> s l7 not 2000-2002/py
TOTAL FOR ALL FILES
L21          5 L7 NOT 2000-2002/PY

=> dup rem l21
PROCESSING COMPLETED FOR L21
L22          1 DUP REM L21 (4 DUPLICATES REMOVED)

=> d ibib abs

L22  ANSWER 1 OF 1     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   1999255424     MEDLINE
DOCUMENT NUMBER:    99255424   PubMed ID: 10320771
TITLE:              Metabolic diversity in myxobacteria: identification of the
                    myxalamid and the stigmatellin biosynthetic gene cluster of
                    Stigmatella aurantiaca Sg a15 and a combined
                    polyketide-(poly)peptide gene cluster from the
                    epothilone producing strain Sorangium cellulosum So
                    ce90.
AUTHOR:             Beyer S; Kunze B; Silakowski B; Muller R
CORPORATE SOURCE:   Gesellschaft fur Biotechnologische Forschung, 38124,
                    Braunschweig, Germany.
SOURCE:             BIOCHIMICA ET BIOPHYSICA ACTA, (1999 May 14) 1445 (2)
                    185-95.
                    Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY:       Netherlands
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        199906
ENTRY DATE:         Entered STN: 19990628
                    Last Updated on STN: 19990628
                    Entered Medline: 19990617
AB   Myxobacterial strains producing polyketides (PKs) assumed to be
     biosynthesized by a type I polyketide synthase (PKS)
     were analysed. Myxobacteria also produce a variety of polypeptides (PP)
     and PKs with incorporated amino acids ('mixed PK-PP'). In order to be able
     to identify the biosynthetic gene clusters for these metabolites a PCR
     based approach has been developed to clone ketosynthase (KS) domains of
     PKS genes from these organisms. Conserved regions of peptide synthetases
     of the non-ribosomal type (NRPS) were also amplified via PCR. KS fragments
     from Stigmatella aurantiaca Sg a15 were used for chromosomal gene
     inactivation experiments resulting in a series of mutants including such
     that were unable to produce stigmatellins and myxalamids. A NRPS fragment
     and PKS fragments from Sorangium cellulosum So ce90 were used to identify
     cosmids hybridizing with both types of probes from a genomic library. Both
     a NRPS and a PKS fragment were cloned and sequenced from a relatively
     short restriction fragment of one of these cosmids. The method described
     here should be very useful to clone and identify PKS, NRPS and mixed
     PKS-NRPS from myxobacteria in general and thereby open opportunities to
     use the biochemical diversity of these bacteria for genetic engineering
     and combinatorial biosynthesis.
```

```
=> dup rem l14
PROCESSING COMPLETED FOR L14
L23           5 DUP REM L14 (2 DUPLICATES REMOVED)

=> d ibib abs 1-5

L23  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2002:484860  CAPLUS
DOCUMENT NUMBER:          137:62265
TITLE:                    Myxococcus host cells for the production of
                          epothilones
INVENTOR(S):              Julien, Bryan; Katz, Leonard; Khosla, Chaitan
PATENT ASSIGNEE(S):       Kosan Biosciences, Inc., USA
SOURCE:                   U.S., 33 pp., Cont.-in-part of U.S. 6,303,342.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   4
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     US 6410301         B1   20020625       US 2000-560367   20000428
     WO 2000031247      A2   20000602       WO 1999-US27438  19991119
     WO 2000031247      A3   20001207
         W:  AL, AM, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE,
             HR, HU, IL, IS, JP, KG, KP, KR, LC, LK, LR, LT, LV, MD, MG, MK,
             MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, ZA, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     US 6303342         B1   20011016       US 1999-443501   19991119
     WO 2001083800      A2   20011108       WO 2001-US13793  20010426
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
             YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                  US 1998-109401P  P  19981120
                                        US 1999-119386P  P  19990210
                                        US 1999-122620P  P  19990303
                                        US 1999-130560P  P  19990422
                                        US 1999-443501   A2 19991119
                                        WO 1999-US27438  A2 19991119
                                        US 2000-560367   A  20000428
                                        US 2000-232696P  P  20000914
                                        US 2000-257517P  P  20001221
                                        US 2001-825856   A  20010403
                                        US 2001-825876   A  20010403
                                        US 2001-269020P  P  20010413
AB   Recombinant Myxococcus host cell contg. recombinant expression vectors
     contg. epothilone polyketide synthase genes
     can produce epothilones C and D but not epothilones A
     and B.
REFERENCE COUNT:          95    THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23  ANSWER 2 OF 5  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2000:368562  CAPLUS
DOCUMENT NUMBER:          133:27369
TITLE:                    Epothilone and epothilone
                          derivatives production based on recombinant nucleic
                          acids encoding the epithilone polyketide
                          synthase from Sorangium cellulosum
INVENTOR(S):              Julien, Bryan; Katz, Leonard; Khosla, Chaitan; Tang,
                          Li; Ziermann, Rainer
```

PATENT ASSIGNEE(S): Kosan Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 138 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000031247	A2	20000602	WO 1999-US27438	19991119
WO 2000031247	A3	20001207		
W: AL, AM, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, IL, IS, JP, KG, KP, KR, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1135470	A2	20010926	EP 1999-960500	19991119
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002530107	T2	20020917	JP 2000-584057	19991119
US 6410301	B1	20020625	US 2000-560367	20000428

PRIORITY APPLN. INFO.:
US 1998-109401P P 19981120
US 1999-119386P P 19990210
US 1999-122620P P 19990303
US 1999-130560P P 19990422
US 1999-443501 A2 19991119
WO 1999-US27438 W 19991119

OTHER SOURCE(S): MARPAT 133:27369

AB Recombinant genomic nucleic acids that encode all or a portion of the **epothilone polyketide synthase** (PKS) from Sorangium cellulosum SMP44 are provided. The epo gene cluster comprises 71,989 bp encoding the loading domain (epoA), the non-ribosomal peptide synthase (NRPS, module 1, epoB), each of the remaining 8 modules of the **epothilone** synthase module (epoC, **epoD**, epoE, and epoF), and the epoK gene that encodes a cytochrome P 450-like epoxidn. enzyme. Recombinant PKS genes are expressed in host cells for the prodn. of **epothilones**, **epothilone** derivs., and polyketides that are useful as cancer chemotherapeutics, fungicides, and immunosuppressants. Two hybrid PKS enzymes are hybrids of deoxyerythronolide B synthase (DEBS) and **epothilone** NRPS module. The first hybrid PKS is composed of 4 proteins: DEBS1; a fusion protein composed of the ketosynthase (KS) domain of module 3 of DEBS and all but the KS domain of the loading domain of the **epothilone** PKS; the **epothilone** NRPS module; and a fusion protein composed of the KS domain of module 2 of the **epothilone** PKS fused to the acyltransferase domain of module 5 of DEBS and the rest of DEBS3. The second hybrid PKS is composed of 5 proteins: DEBS1, a fusion protein composed of the KS domain of module 3 of DEBS and all but the KS domain of the **epothilone** PKS loading domain; the **epothilone** NRPS module; a fusion protein composed of the KS domain of module 2 of **epothilone** PKS fused to the AT domain of module 4 of DEBS and the ret of DEBS2; and DEBS3. Novel epithilone derivs. are produced where these hybrid PKS are expressed in Streptomyces coelicolor or Saccharopolyspora erythraea.

L23 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:88787 CAPLUS
DOCUMENT NUMBER: 132:289462
TITLE: Cloning and heterologous expression of the **epothilone** gene cluster
AUTHOR(S): Tang, Li; Shah, Sanjay; Chung, Loleta; Carney, John; Katz, Leonard; Khosla, Chaitan; Julien, Bryan
CORPORATE SOURCE: KOSAN Biosciences, Hayward, CA, 94545, USA
SOURCE: Science (Washington, D. C.) (2000), 287(5453), 640-642
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The polyketide **epothilone** is a potential anticancer agent that stabilizes microtubules in a similar manner to Taxol. The gene cluster responsible for **epothilone** biosynthesis in the myxobacterium Sorangium cellulosum was cloned and completely sequenced. It encodes six multifunctional proteins composed of a loading module, one nonribosomal peptide synthetase module, eight **polyketide synthase** modules, and a P 450 epoxidase that converts desoxyepothilone into **epothilone**. Concomitant expression of these genes in the actinomycete Streptomyces coelicolor produced **epothilones** A and B. Streptomyces coelicolor is more amenable to strain improvement and grows about 10-fold as rapidly as the natural producer, so this heterologous expression system portends a plentiful supply of this important agent.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 4 OF 5 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000293058 MEDLINE
DOCUMENT NUMBER: 20293058 PubMed ID: 10831849
TITLE: Isolation and characterization of the **epothilone** biosynthetic gene cluster from Sorangium cellulosum.
AUTHOR: Julien B; Shah S; Ziermann R; Goldman R; Katz L; Khosla C
CORPORATE SOURCE: Kosan Biosciences, Inc., Hayward, CA 94545, USA.. julien@kosan.com
CONTRACT NUMBER: 1 R43 CA79228-01 (NCI)
SOURCE: GENE, (2000 May 16) 249 (1-2) 153-60.
Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF217189
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000728
Last Updated on STN: 20000728
Entered Medline: 20000720

AB The **epothilone** biosynthetic gene cluster was isolated from Sorangium cellulosum strain SMP44. The gene cluster contains seven genes and spans approx. 56kb. The genes encoding the PKS, epoA, epoC, **epoD**, epoE, and epoF, are divided into nine modules. The EpoB protein is a non-ribosomal peptide synthetase (NRPS) that catalyzes formation of the thiazole found in the **epothilones**. EpoK is a P450 enzyme responsible for the epoxidation of **epothilones** C and D to **epothilones** A and B, respectively. EpoK was expressed in Escherichia coli, and the purified protein was shown to convert **epothilone** D to **epothilone** B in vitro.

L23 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:811346 CAPLUS
DOCUMENT NUMBER: 132:60132
TITLE: Genes for the biosynthesis of **epothilones** by Sorangium cellulosum
INVENTOR(S): Schupp, Thomas; Ligon, James Madison; Molnar, Istvan; Zirkle, Ross; Gorlach, Jorn; Cyr, Devon
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft mbH
SOURCE: PCT Int. Appl., 174 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966028	A2	19991223	WO 1999-EP4171	19990616
WO 9966028	A3	20000629		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,

TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2329774	AA	19991223	CA 1999-2329774	19990616
AU 9946116	A1	20000105	AU 1999-46116	19990616
BR 9911349	A	20010313	BR 1999-11349	19990616
EP 1088078	A2	20010404	EP 1999-929243	19990616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO				
JP 2002518004	T2	20020625	JP 2000-554837	19990616
US 6121029	A	20000919	US 1999-335409	19990617
US 6346404	B1	20020212	US 2000-568102	20000510
US 6355457	B1	20020312	US 2000-567969	20000510
US 6355458	B1	20020312	US 2000-568480	20000510
US 6355459	B1	20020312	US 2000-568486	20000510
US 6358719	B1	20020319	US 2000-568472	20000510
US 6383787	B1	20020507	US 2000-567899	20000510
NO 2000006195	A	20010216	NO 2000-6195	20001206

PRIORITY APPLN. INFO.:	US 1998-155183P	P	19980618
	US 1998-99504	A	19980618
	US 1998-101631P	P	19980924
	US 1999-118906P	P	19990205
	WO 1999-EP4171	W	19990616
	US 1999-335409	A3	19990617

AB Nucleic acid mols. are isolated from Sorangium cellulosum that encode polypeptides necessary for the biosynthesis of **epothilone** in Sorangium cellulosum strain 90 (DSM 6773). The gene cluster includes 22 open reading frames, several of which include domains for a given distinct activity of the **epothilone** synthase, including acyl carrier protein, .beta.-ketosynthase, acyltransferase, .beta.-ketoreductase, dehydratase, enoyl reductase, and thioesterase. Disclosed are methods for the prodn. of **epothilone** in recombinant hosts transformed with the genes of the invention. In this manner, **epothilone** can be produced in quantities large enough to enable their purifn. and use in pharmaceutical formulations such as those for the treatment of cancer.

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=> s epothilone and (gene or clon? or dna or cdna or nucleic acid sequence)
TOTAL FOR ALL FILES
L30        186 EPOTHILONE AND (GENE OR CLON? OR DNA OR CDNA OR NUCLEIC ACID
               SEQUENCE)

=> s l30 not 2000-2002/py
TOTAL FOR ALL FILES
L37         37 L30 NOT 2000-2002/PY

=> dup rem l37
PROCESSING COMPLETED FOR L37
L38         13 DUP REM L37 (24 DUPLICATES REMOVED)

=> d ibib abs 1-13

L38  ANSWER 1 OF 13     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   1999238324     MEDLINE
DOCUMENT NUMBER:    99238324   PubMed ID: 10220336
TITLE:              The coral-derived natural products eleutherobin and
                    sarcodictyins A and B: effects on the assembly of purified
                    tubulin with and without microtubule-associated proteins
                    and binding at the polymer taxoid site.
AUTHOR:             Hamel E; Sackett D L; Vourloumis D; Nicolaou K C
CORPORATE SOURCE:   Laboratory of Drug Discovery Research and Development,
                    National Cancer Institute, Frederick Cancer Research and
                    Development Center, Maryland 21702, USA.
SOURCE:             BIOCHEMISTRY, (1999 Apr 27) 38 (17) 5490-8.
                    Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
```

ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990601
Last Updated on STN: 19990601
Entered Medline: 19990514

AB We examined interactions with purified tubulin of synthetic sarcodictyins A and B and eleutherobin (coral-derived antimitotic agents) and of compound 1, an analogue of sarcodictyin A methylated at the C-3 oxygen atom (i.e., the methyl ketal analogue of sarcodictyin A and thus structurally similar to eleutherobin but lacking the C-3 sugar moiety). Eleutherobin was much more active than sarcodictyins A and B, which were somewhat more active than compound 1. Effects of eleutherobin did not differ greatly from those of paclitaxel and **epothilone** A. Eleutherobin and **epothilone** A were competitive inhibitors of the binding of radiolabeled paclitaxel to tubulin polymer (apparent Ki values of 2.1 and 2.6 microM, respectively). Tubulin assembly reactions induced by all compounds were similar to the paclitaxel-driven reactions in being enhanced by the addition of microtubule-associated proteins and/or GTP to the reaction mixture and by progressively higher reaction temperatures. Antiproliferative activity was studied in six human cancer cell lines, including two paclitaxel-resistant lines with point mutations in a beta-tubulin **gene**. Except for compound 1, effects on cell growth were generally in accord with effects on purified tubulin. Thus, sarcodictyins A and B had IC50 values in the 200-500 nM range; paclitaxel, <10 nM (except in the resistant lines); and eleutherobin and **epothilone** A, 10-40 nM. The antiproliferative activity of compound 1 was more comparable to that of eleutherobin than sarcodictyin A, despite its weak interaction with tubulin. The activities of the sarcodictyins, eleutherobin, and compound 1 in the mutant ovarian lines were similar to their activities in the parental line.

L38 ANSWER 2 OF 13 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999084660 EMBASE
TITLE: Mechanisms of action of and resistance to antitubulin agents: Microtubule dynamics, drug transport, and cell death.
AUTHOR: Dumontet C.; Sikic B.I.
CORPORATE SOURCE: Dr. C. Dumontet, Service d'Hematologie, Centre Hospitalier Lyon Sud, 69495 Pierre Benite Cedex, France. cd@hematologie.univ-lyon1.fr
SOURCE: Journal of Clinical Oncology, (1999) 17/3 (1061-1070). Refs: 116
ISSN: 0732-183X CODEN: JCONDN
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Purpose: To analyze the available data concerning mechanisms of action of and mechanisms of resistance to the antitubulin agents, vinca alkaloids and taxanes, and more recently described compounds. Design: We conducted a review of the literature on classic and recent antitubulin agents, focusing particularly on the relationships between antitubulin agents and their intracellular target, the soluble tubulin/microtubule complex. Results and Conclusion: Although it is widely accepted that antitubulin agents block cell division by inhibition of the mitotic spindle, the mechanism of action of antitubulin agents on microtubules remains to be determined. The classic approach is that vinca alkaloids depolymerize microtubules, thereby increasing the soluble tubulin pool, whereas taxanes stabilize microtubules and increase the microtubular mass. More recent data suggest that both classes of agents have a similar mechanism of action, involving the inhibition of microtubule dynamics. These data suggest that vinca alkaloids and taxanes may act synergistically as antitumor agents and maybe administered as combination chemotherapy in the clinic. However, enhanced myeloid and neurologic toxicity, as well as a strong dependence on the sequence of administration, presently exclude these combinations outside the context of clinical trials. Although the multidrug resistance phenotype mediated by Pgp appears to be an important mechanism of resistance to these agents, alterations of microtubule structure resulting in altered microtubule dynamics and/or altered binding

of antitubulin agents may constitute a significant mechanism of drug resistance.

L38 ANSWER 3 OF 13 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999249131 EMBASE
TITLE: [New approaches in cancer therapy].
NEUE THERAPIEANSATZE BEI KREBS: EDITORIAL.
AUTHOR: Heinzl S.
SOURCE: Medizinische Monatsschrift fur Pharmazeuten, (1999) 22/7 (197).
ISSN: 0342-9601 CODEN: MMPHDB
COUNTRY: Germany
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: German

L38 ANSWER 4 OF 13 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999255424 MEDLINE
DOCUMENT NUMBER: 99255424 PubMed ID: 10320771
TITLE: Metabolic diversity in myxobacteria: identification of the myxalamid and the stigmatellin biosynthetic **gene** cluster of Stigmatella aurantiaca Sg a15 and a combined polyketide-(poly)peptide **gene** cluster from the **epothilone** producing strain Sorangium cellulosum So ce90.
AUTHOR: Beyer S; Kunze B; Silakowski B; Muller R
CORPORATE SOURCE: Gesellschaft fur Biotechnologische Forschung, 38124, Braunschweig, Germany.
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1999 May 14) 1445 (2) 185-95.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 19990628
Entered Medline: 19990617
AB Myxobacterial strains producing polyketides (PKs) assumed to be biosynthesized by a type I polyketide synthase (PKS) were analysed. Myxobacteria also produce a variety of polypeptides (PP) and PKs with incorporated amino acids ('mixed PK-PP'). In order to be able to identify the biosynthetic **gene** clusters for these metabolites a PCR based approach has been developed to **clone** ketosynthase (KS) domains of PKS **genes** from these organisms. Conserved regions of peptide synthetases of the non-ribosomal type (NRPS) were also amplified via PCR. KS fragments from Stigmatella aurantiaca Sg a15 were used for chromosomal **gene** inactivation experiments resulting in a series of mutants including such that were unable to produce stigmatellins and myxalamids. A NRPS fragment and PKS fragments from Sorangium cellulosum So ce90 were used to identify cosmids hybridizing with both types of probes from a genomic library. Both a NRPS and a PKS fragment were **cloned** and sequenced from a relatively short restriction fragment of one of these cosmids. The method described here should be very useful to **clone** and identify PKS, NRPS and mixed PKS-NRPS from myxobacteria in general and thereby open opportunities to use the biochemical diversity of these bacteria for genetic engineering and combinatorial biosynthesis.

L38 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 3
ACCESSION NUMBER: 1998:236082 CAPLUS
DOCUMENT NUMBER: 129:12364
TITLE: Taxane-mediated **gene** induction is independent of microtubule stabilization: induction of transcription regulators and enzymes that modulate inflammation and apoptosis
AUTHOR(S): Moos, Philip J.; Fitzpatrick, F. A.
CORPORATE SOURCE: Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, 84108, USA
SOURCE: Proceedings of the National Academy of Sciences of the

United States of America (1998), 95(7), 3896-3901
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Pharmacol. traits of the antineoplastic agent taxol may originate in part from its effects on **gene** expression and not simply from its effects on microtubule assembly. This prompts three questions. First, how extensive is **gene** induction by taxol. Second, is **gene** induction confined to taxol itself, or does it occur with other taxane analogs. Third, do the functions of any induced **genes** correspond with known attributes of taxol or taxane analogs. We report that taxol induces numerous early-response **genes**, not just cytokine **genes**. Previously unidentified taxol-induced **genes** include **genes** coding transcription factors with tumor suppressor effects (krox-24) and enzymes that govern proliferation, apoptosis, and inflammation (2',5'-oligoadenylate synthase, cyclooxygenase-2, and an I.kappa.B kinase termed chuk). Taxotere, a potent analog of taxol, did not induce any of these **genes**, implying that taxol modulates **gene** expression by a mechanism that is distinct from microtubule stabilization and cell cycle arrest. Other taxane analogs induce some of the same **genes** as taxol, indicating that this process is not unique to taxol. Functional changes coincided with changes in **gene** expression. For instance, induction of tumor necrosis factor .alpha. (TNF.alpha.) accentuated apoptosis in cells treated with taxol compared with corresponding cells treated with taxotere. The functions of several induced **genes** (e.g., krox-24 and cyclooxygenase-2) are self-consistent with beneficial and adverse effects encountered during taxol administration. These results may be relevant to the safe and effective use of taxol or its analogs in oncol. and other areas of medicine.

L38 ANSWER 6 OF 13 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998132596 MEDLINE
DOCUMENT NUMBER: 98132596 PubMed ID: 9465021
TITLE: Farnesyl transferase inhibitors cause enhanced mitotic sensitivity to taxol and **epothilones**.
AUTHOR: Moasser M M; Sepp-Lorenzino L; Kohl N E; Oliff A; Balog A; Su D S; Danishefsky S J; Rosen N
CORPORATE SOURCE: Department of Medicine, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA.
CONTRACT NUMBER: P50CA68425-02 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Feb 17) 95 (4) 1369-74. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980326
Last Updated on STN: 19980326
Entered Medline: 19980319

AB An important class of cellular proteins, which includes members of the p21ras family, undergoes posttranslational farnesylation, a modification required for their partition to membranes. Specific farnesyl transferase inhibitors (FTIs) have been developed that selectively inhibit the processing of these proteins. FTIs have been shown to be potent inhibitors of tumor cell growth in cell culture and in murine models and at doses that cause little toxicity to the animal. These data suggest that these drugs might be useful therapeutic agents. We now report that, when FTI is combined with some cytotoxic antineoplastic drugs, the effects on tumor cells are additive. No interference is noted. Furthermore, FTI and agents that prevent microtubule depolymerization, such as taxol or **epothilones**, act synergistically to inhibit cell growth. FTI causes increased sensitivity to induction of metaphase block by these agents, suggesting that a farnesylated protein may regulate the mitotic check point. The findings imply that FTI may be a useful agent for the treatment of tumors with wild-type ras that are sensitive to taxanes.

L38 ANSWER 7 OF 13 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999201088 MEDLINE
DOCUMENT NUMBER: 99201088 PubMed ID: 10099292
TITLE: Directed evolution of an esterase for the stereoselective resolution of a key intermediate in the synthesis of **epothilones**.
AUTHOR: Bornscheuer U T; Altenbuchner J; Meyer H H
CORPORATE SOURCE: Institute for Technical Biochemistry, University of Stuttgart, Allmandring 31, 70569 Stuttgart, Germany.. itbubo@po.unij-stuttgart.de
SOURCE: BIOTECHNOLOGY AND BIOENGINEERING, (1998 Jun 5) 58 (5) 554-9.
Journal code: 7502021. ISSN: 0006-3592.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990517
Last Updated on STN: 19990517
Entered Medline: 19990503

AB The directed evolution of an esterase from Pseudomonas fluorescens using the mutator strain Epicurian coli XL1-Red was investigated. Mutants were assayed for their ability to hydrolyze a sterically hindered 3-hydroxy ester, which can serve as a building block in the synthesis of **epothilones**. Screening was performed by plating esterase producing colonies derived from mutation cycles onto minimal media agar plates containing indicator substances (neutral red and crystal violet). Esterase-catalyzed hydrolysis of the 3-hydroxy ester (ethyl or glycerol ester) was detected by the formation of a red color due to a pH decrease caused by the released acid. Esterases isolated from positive **clones** were used in preparative biotransformations of the ethyl ester. One variant containing two mutations (A209D and L181V) stereoselectively hydrolyzed the ethyl ester resulting in 25% ee for the remaining ester.
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L38 ANSWER 8 OF 13 MEDLINE
ACCESSION NUMBER: 1999059488 MEDLINE
DOCUMENT NUMBER: 99059488 PubMed ID: 9845355
TITLE: Upregulation of caveolin-1 and caveolae organelles in Taxol-resistant A549 cells.
AUTHOR: Yang C P; Galbiati F; Volonte D; Horwitz S B; Lisanti M P
CORPORATE SOURCE: Department of Molecular Pharmacology and The Albert Einstein Cancer Center, Albert Einstein College of Medicine, Bronx, NY 10461, USA.
CONTRACT NUMBER: CA13330 (NCI)
CA39821 (NCI)
GM-50443 (NIGMS)
SOURCE: FEBS LETTERS, (1998 Nov 20) 439 (3) 368-72.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000901
Entered Medline: 19981221

AB Caveolin is a principal component of caveolae membranes. It has been demonstrated that the interaction of the caveolin scaffolding domain with signaling molecules can functionally inhibit the activity of these molecules. Taxol is an antitumor agent that suppresses microtubule dynamics and binds to microtubules thereby stabilizing them against depolymerization. The drug also has been implicated in the induction of apoptosis through activation of components in signal transduction cascades. Here we have investigated the role of caveolin in the development of drug resistance by examining the expression of caveolins in low- and high-level drug-resistant cell lines. Caveolin-1, but not caveolin-2, was upregulated in highly multidrug resistant SKVLBI cells that express high levels of P-glycoprotein, and in low-level

Taxol-resistant A549 cell lines that express low amounts of P-glycoprotein. Two drug-resistant A549 cell lines (one 9-fold resistant to Taxol and the other 1.5-fold resistant to **epothilone** B), both of which express no P-glycoprotein, demonstrate a significant increase in the expression of caveolin-1. These results indicate that in low-level **epothilone** B- or Taxol-resistant A549 cells, increased caveolin-1 expression occurs independently of P-glycoprotein expression. Electron microscopic studies clearly demonstrate the upregulation of caveolae organelles in Taxol-resistant A549 cells. Upregulation of caveolin-1 expression in drug-sensitive A549 cells was observed acutely beginning 48 h after incubation with 10 nM Taxol. Thus, caveolin-1 may play a role in the development of Taxol resistance in A549 cells.

L38 ANSWER 9 OF 13 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1998:304419 SCISEARCH
THE GENUINE ARTICLE: ZG989
TITLE: Plasmodium falciparum: Characterization of organelle migration during merozoite morphogenesis in asexual malaria infections
AUTHOR: Taraschi T F (Reprint); Trelka D; Schneider T; Matthews I
CORPORATE SOURCE: THOMAS JEFFERSON UNIV, JEFFERSON MED COLL, DEPT PATHOL ANAT & CELL BIOL, 1020 LOCUST ST, PHILADELPHIA, PA 19107 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: EXPERIMENTAL PARASITOLOGY, (MAR 1998) Vol. 88, No. 3, pp. 184-193.
Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.
ISSN: 0014-4894.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 27

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Treatment of asexual Plasmodium falciparum infections with the microtubule stabilizing agents Taxol or **epothilone** A prevents the depolymerization of nuclear microtubules. Serial thin sectioning of treated parasites revealed the presence of polymerized nuclear microtubule assemblies extending from spindle pole bodies into the forming merozoites in late stage infections. This organization prevented daughter merozoites from pinching off the mother schizont during merogony. An electron-dense collar was apparent nt at the junction of the budding parasites and the schizont plasma membrane, suggesting the presence of a contractile, actin-myosin ring. Examination of Taxol or EpA arrested parasites provided new information about the merogonic process and the control of organelle migration. Drug treatment did nor affect the migration or polarity of the rhoptries and micronemes. Ultrastructural characterization of drug-treated trophozoites identified an assembly of smooth vesicles and short tubules adjacent to the parasite nuclei. During merogony, these membranes were observed as flattened cisternae with dilated rims that appeared to be coated. The morphology and location of these membranes suggest that they may be the parasite Golgi apparatus. This investigation reveals that the antimalarial activity of microtubule stabilizing agents is due to their inhibition of merozoite formation. (C) 1998 Academic Press.

L38 ANSWER 10 OF 13 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998398507 EMBASE
TITLE: [For research and practice. Report of the Annual Meeting 1998 of the German Pharmaceutical Society]. FUR WISSENSCHAFT UND PRAXIS. BERICHT VON DER DPHG-JAHRESTAGUNG 1998.
AUTHOR: Blasius H.; Ditzel P.; Rall B.; Schmidt R.
SOURCE: Deutsche Apotheker Zeitung, (12 Nov 1998) 138/46 (54-69).
ISSN: 0011-9857 CODEN: DAZEA2
COUNTRY: Germany
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 003 Endocrinology
004 Microbiology
016 Cancer
017 Public Health, Social Medicine and Epidemiology
030 Pharmacology

037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: German

L38 ANSWER 11 OF 13 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97347524 MEDLINE
DOCUMENT NUMBER: 97347524 PubMed ID: 9202030
TITLE: Paclitaxel-resistant human ovarian cancer cells have mutant beta-tubulins that exhibit impaired paclitaxel-driven polymerization.
AUTHOR: Giannakakou P; Sackett D L; Kang Y K; Zhan Z; Buters J T; Fojo T; Poruchynsky M S
CORPORATE SOURCE: Medicine Branch, Division of Clinical Sciences, NCI, National Institutes of Health, Bethesda, Maryland 20892, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jul 4) 272 (27) 17118-25.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970812
Last Updated on STN: 19970812
Entered Medline: 19970731
AB Acquired resistance to paclitaxel can be mediated by P-glycoprotein or by alterations involving tubulin. We report two paclitaxel-resistant sublines derived from 1A9 human ovarian carcinoma cells. Single-step paclitaxel selection with verapamil yielded two **clones** that are resistant to paclitaxel and collaterally sensitive to vinblastine. The resistant sublines are not paclitaxel-dependent, and resistance remained stable after 3 years of drug-free culture. All cell lines accumulate [3H]paclitaxel equally, and no MDR-1 mRNA was detected by polymerase chain reaction following reverse transcription. Total tubulin content is similar, but the polymerized fraction increased in parental but not in resistant cells following the paclitaxel addition. Purified tubulin from parental cells demonstrated paclitaxel-driven increased polymerization, in contrast to resistant cell tubulin, which did not polymerize under identical conditions. In contrast, **epothilone** B, an agent to which the resistant cells retained sensitivity, increased assembly. Comparable expression of beta-tubulin isotypes was found in parental and resistant cells, with predominant expression of the M40 and beta2 isotypes. Sequence analysis demonstrated acquired mutations in the M40 isotype at nucleotide 810 (T --> G; Phe270 --> Val) in 1A9PTX10 cells and nucleotide 1092 (G --> A; Ala364 --> Thr) in 1A9PTX22 cells. These results identify residues beta270 and beta364 as important modulators of paclitaxel's interaction with tubulin.

L38 ANSWER 12 OF 13 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97014958 EMBASE
DOCUMENT NUMBER: 1997014958
TITLE: Raf-1/bcl-2 phosphorylation: A step from microtubule damage to cell death.
AUTHOR: Blagosklonny M.V.; Giannakakou P.; El-Deiry W.S.; Kingston D.G.I.; Higgs P.I.; Neckers L.; Fojo T.
CORPORATE SOURCE: T. Fojo, Medicine Branch, NIH, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892, United States
SOURCE: Cancer Research, (1997) 57/1 (130-135).
Refs: 40
ISSN: 0008-5472 CODEN: CNREA8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Recent studies have shown that paclitaxel leads to activation of Raf-1 kinase and have suggested that this activation is essential for bcl-2

phosphorylation and apoptosis. In the present study, we demonstrate that, in addition to paclitaxel, other agents that interact with tubulin and microtubules also induce Raf-1/bcl-2 phosphorylation, whereas **DNA** -damaging drugs, antimetabolites, and alkylating agents do not. Activation of Raf-1 kinase by paclitaxel is linked to tubulin polymerization; the effect is blunted in paclitaxel-resistant cells, the tubulin of which does not polymerize following the addition of paclitaxel. In contrast, vincristine and vinblastine, drugs to which the paclitaxel-resistant cells retain sensitivity were able to bring about Raf-1 phosphorylation. The requirement for disruption of microtubules in this signaling cascade was strengthened further using paclitaxel analogues by demonstrating a correlation between tubulin polymerization, Raf-1/bcl-2 phosphorylation, and cytotoxicity. Inhibition of RNA or protein synthesis prevents Raf-1 activation and bcl-2 phosphorylation, suggesting that an intermediate protein(s) acts upstream of Raf-1 in this microtubule damage-activating pathway. A model is proposed that envisions a pathway of Raf-1 activation and bcl-2 phosphorylation following disruption of microtubular architecture, serving a role similar to p53 induction following **DNA** damage.

L38 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 7
ACCESSION NUMBER: 1997:445231 CAPLUS
DOCUMENT NUMBER: 127:117170
TITLE: **Epothilone** A induces apoptosis in neuroblastoma cells with multiple mechanisms of drug resistance
AUTHOR(S): Wolff, Armin; Technau, Antje; Brandner, Gerhard
CORPORATE SOURCE: Abteilung Virologie, Institut fur Medizinische Mikrobiologie und Hygiene der Universitat, Freiburg, D-79008, Germany
SOURCE: International Journal of Oncology (1997), 11(1), 123-126
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Epothilone** A, a novel macrolide antibiotic, is produced by the myxobacterium Sorangium cellulosum. Similarly to paclitaxel (Taxol), **epothilone** A inhibits cell proliferation and induces apoptosis by binding to tubulin and stabilizing of microtubuli. Like paclitaxel, **epothilone** A induced apoptosis in neuroblastoma cells which exhibit constitutive cytoplasmic sequestration of p53 and, hence, an impaired **DNA**-damage-dependent apoptosis. However, in contrast to paclitaxel, **epothilone** A was also effective against a constitutively Pgp-expressing, multidrug resistant neuroblastoma cell line (SK-N-SH). Moreover, the efficacy of **epothilone** A was not impaired even though the Pgp level was further increased during treatment with the drug.

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